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REPLY TO Wilmington Office

December 1, 2006

VIA ECF
The Honorable Kent A. Jordan
United States District Court
District of Delaware
844 North King Street
Wilmington, DE 19801

Re: *Glaxo Group Limited v. Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries Limited*, No. 04-CV-171 (KAJ)

Dear Judge Jordan:

We represent plaintiff Glaxo Group Limited ("Glaxo") in the above-referenced patent infringement action brought pursuant to the Hatch-Waxman Act. As your Honor is aware, there are various summary judgment motions *sub judice*. We write to inform the Court, pursuant to Local Rule 7.1.2(c), of a very recent Federal Circuit decision that bears directly on the parties' motions for summary judgment on the issue of infringement under the doctrine of equivalents.

On November 15, 2006, the Federal Circuit decided *Abraxis Bioscience, Inc. v. Mayne Pharma (USA) Inc.*, Civ. No. 06-1118 (Fed. Cir. Nov. 15, 2006). A copy of the opinion is attached. In *Abraxis*, the patent-in-suit was directed to an improved pharmaceutical formulation of DIPRIVAN®, a drug containing propofol as the active ingredient and used to induce and maintain general anesthesia and sedation in patients. *Abraxis*, Slip. Op. at 2. The inventors, trying to solve a problem with increased frequency of post-operative bacterial infections in DIPRIVAN® patients, "discovered that one preservative in particular, disodium edetate, was unexpectedly effective in retarding microbial growth in the propofol formulation . . . ." *Id.* at 2-3. The patent for the improved DIPRIVAN® formulation claimed "[a] sterile pharmaceutical composition for parenteral administration . . . which further comprises an amount of edetate sufficient to prevent a no more than 10-fold increase in growth of [listed bacteria] . . . ." *Id.* at 7.

The defendant in *Abraxis* sought to market a generic version of the improved DIPRIVAN® formulation by substituting an antimicrobial preservative called calcium trisodium DTPA in place of the claimed "edetate" (a/k/a "EDTA") preservative. *Abraxis*, Slip. Op. at 4-5. Because the parties agreed that calcium trisodium DTPA was not a derivative of EDTA, the Federal Circuit held that there was no literal infringement of the claims in the patent-in-suit. *Id.* at 13. The *Abraxis* case, therefore, turned on the doctrine of equivalents.

The Federal Circuit approved the district court's "well-reasoned opinion" utilizing the function-way-result test of *Graver Tank & Mfg. Co. v. Linde Air Products Co.*, 339 U.S. 605, 609 (1950), to find equivalence. *Abraxis,* Slip. Op. at 15. Although the Federal Circuit found that defendant had waived its arguments concerning the function and result prongs of the test, *id.* at 16 n.8, it noted with tacit approval the district court's very closely related definitions of the function of edetate "as 'retarding microbial growth in propofol oil-in-water emulsions,'" and "that the result achieved was 'retard[ing] microbial growth to the extent required by the microbiological test set forth in the claim.'" *Id.* at 15. This is precisely analogous to the '249 patent's description of the function of ethanol as chemically enhancing the stability of ranitidine in the claimed aqueous formulation for oral administration, with the resulting pharmaceutical formulation therefore having the enhanced stability, *i.e.*, improved shelf-life of the drug product. ('249 Patent Col. 1:40-56; Sept. 8, 2006 Oral Arg. Tr. at 43:22-45:19); *Glaxo Wellcome, Inc. v. Pharmadyne Corp.*, 32 F. Supp. 2d 265, 285 (D. Md. 1998).

The Federal Circuit also found that the district court had properly determined that the "way" in which both EDTA and calcium trisodium DTPA performed their function of retarding microbial growth in the formulation was by metal ion chelation. *Abraxis*, Slip Op. at 15-16. Defendant contended that the proper definition of "way" was a much narrower, more specific definition, "*i.e.*, one that incorporates the specific metal ions that are chelated, the strength of the bonds that are formed during chelation, and the stability constants." *Id.* at 16. Because plaintiff did not offer infringement evidence to establish these additional specific factors, defendant argued that there was a failure of proof of infringement. *Id.* In the present case, defendant Teva has taken an analogous position arguing that the "way" in which ethanol and propylene glycol function requires proof of a specific chemical pathway to stabilize ranitidine rather than simply by using ethanol or propylene glycol to inhibit ranitidine degradation. (Sept. 8, 2006 Oral Arg. Tr. at 41:10-42:3, 46:12-47:11). Contrary to the argument of the defendant in *Abraxis*, and Teva here, the Federal Circuit held that the "way" EDTA functioned was not so narrow and specific and had been properly defined by the district court with reference to the *context* of the patent-in-suit. *Abraxis*, Slip. Op. at 16-17.

Glaxo's U.S. Patent No. 5,068,249 ("the '249 patent") describes the function of ethanol as chemically enhancing the stability of ranitidine in an aqueous formulation for oral administration. ('249 Patent Col. 1:39-44). This is in contrast to physically stabilizing ranitidine by, for example, refrigeration (inhibiting thermal degradation) or packaging the drug product in a dark bottle (inhibiting degradation from exposure to light). The way in which that function is accomplished is by adding a chemical—ethanol—to the formulation to inhibit ranitidine degradation where, in an *aqueous formulation* for oral administration, the ethanol will inhibit hydrolysis (degradation from exposure to water) and/or oxidation (degradation from exposure to oxygen) of ranitidine. (*Id.* at Col. 1:39-44, 54-60; Kibbe Dep. at 18:9-20:12, Langer Decl. (D.I. 99 and 100), Ex. 24; Kibbe Dep. at 120:11-121:20, 145:1-149:11, 178:18-181:2, Langer 2d Suppl. Decl. (D.I. 149), Ex. 7; Anderson Suppl. Rpt. ¶¶ 16-21, Anderson Decl. (D.I. 98), Ex. C); s*ee Pharmadyne*, 32 F. Supp. 2d at 285-286 ("Despite Drs. Wray and Long's failure to

understand the exact mechanics of how ethanol stabilizes ranitidine hydrochloride, both reached the conclusion that ranitidine degrades through hydrolysis and that ethanol retards the hydrolytic process. Dr. Long is not required to understand the exact mechanics of his invention, so long as the '249 patent discloses to the ordinary formulator how to make and use the invention.") (citations omitted). Accordingly, the proper infringement analysis of the "way" requires only a determination of whether propylene glycol, substituted in place of ethanol in Teva's ANDA product, chemically enhances the stability of ranitidine by inhibiting ranitidine degradation in the aqueous formulation for oral administration. It is undisputed that both ethanol and propylene glycol chemically enhance the stability of ranitidine by inhibiting hydrolytic and/or oxidative degradation of ranitidine in an aqueous formulation for oral administration. (Kibbe Dep. at 18:9-20:12, Langer Decl. (D.I. 99 and 100), Ex. 24; Kibbe Dep. at 118:2-120:10, 145:1-149:11, 178:18-181:2, 193:7-194:6, Langer 2d Suppl. Decl. (D.I. 149), Ex. 7; Anderson Opening Rpt. ¶¶ 80-84, Anderson Decl. (D.I. 98), Ex. A; Anderson Suppl. Rpt. ¶¶ 16-21, Anderson Decl. (D.I. 98), Ex. C).

Teva's only argument is that, despite the fact that both ethanol-stabilized and propylene glycol-stabilized formulations produce the same ranitidine degradation impurities, propylene glycol must be working in a different "way" than ethanol because the specific amounts of those identical impurities are slightly different. (Sept. 8, 2006 Oral Arg. Tr. at 46:12-47:11). In *Abraxis*, however, the Federal Circuit held that such a narrow, specific standard is not required under the doctrine of equivalents. *Abraxis*, Slip Op. at 15-17. Rather, as held in *Abraxis*, it is sufficient for Glaxo to show by a preponderance of the evidence that propylene glycol chemically enhances the stability of ranitidine in the same way as ethanol by inhibiting the hydrolysis and/or oxidation of ranitidine in an aqueous formulation for oral administration. There is no legal requirement for anything more specific to satisfy the "way" prong of *Graver Tank's* function-way-result test.

The second point for which the *Abraxis* decision is pertinent to the parties' summary judgment motions is the Federal Circuit's rejection of the defendant's argument that "it was impermissible as a matter of law for the meaning of edetate to extend to calcium trisodium DTPA by equivalence because the patentees chose to narrowly claim their invention." *Abraxis*, Slip Op. at 14. That is the identical "public policy" type of argument made by Teva in this case. (Sept. 8, 2006 Oral Arg. Tr. at 63:7-69:22). Teva has argued that Glaxo "had an option to broaden their claim or to narrow their claim, ethanol with a subset or ethanol, [within] a broader class of chemicals. Based on the prior art of record, they narrowed [it to] ethanol and I believe they gave up the rest of the lower aliphatic alcohols . . .". (*Id.* at 69:16-22). The Federal Circuit rejected the identical argument in *Abraxis*:

> Secondly, we reject Mayne's argument that, as a matter of law, it is impermissible for the meaning of edetate to extend to other polyaminocarboxylates by equivalence. Mayne contends that by claiming their invention narrowly, i.e., by limiting the claim to edetate, Abraxis is barred from capturing DTPA, or any

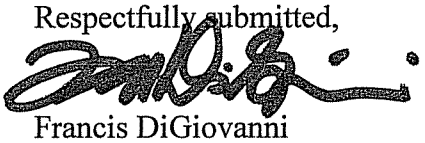
> other polyaminocarboxylate, as an equivalent. * * * There is no evidence that the patentees made a clear and unmistakable surrender of other polyaminocarboxylates, or calcium trisodium DTPA in particular, during prosecution.

Abraxis, Slip Op. at 17-18. The Federal Circuit also distinguished defendant Mayne's reliance on *Tanabe Seiyaku Co. v. United States International Trade Commission*, 109 F.3d 726 (Fed. Cir. 1997), the same case relied on by Teva. *Abraxis*, Slip. Op. at 17-18. The Federal Circuit, therefore, found that the inventors did not clearly disavow other polyaminocarboxylates merely by restricting their patent claim to edetate. *Id.*

The Federal Circuit held that it was the "very unforeseeability" of substituting calcium trisodium DTPA in place of EDTA during the period of patent prosecution that supported the finding of infringement by equivalents. *Id.* at 18-19. Here, the unforeseeability of substituting propylene glycol in place of ethanol as a ranitidine stabilizer during the period of the '249 patent's prosecution has been acknowledged by both parties. (Kibbe Dep. at 87:18-88:9, 89:22-91:21, 92:24-93:19, Langer 2d Suppl. Decl. (D.I. 149), Ex. 7; Anderson Rebuttal Rpt. ¶¶ 28, 34, 41, 57, Anderson Decl. (D.I. 98), Ex. B; Long Decl. (D.I. 126), ¶¶ 15, 18-19); *see also Pharmadyne*, 32 F. Supp. 2d at 290-91 ("Nothing in the prosecution history of the '249 patent shows that Glaxo considered the use of propylene glycol or any other constituent as a stabilizer."). This acknowledgement supports the conclusion that Glaxo did not waive its right to claim equivalents beyond ethanol.

In sum, the doctrine of equivalents is designed to protect inventors from unscrupulous copyists and unanticipated equivalents. *Abraxis*, Slip Op. at 19 (citations omitted). Teva's proposed ANDA product infringes Glaxo's '249 patent under the doctrine of equivalents because Teva's substitution of propylene glycol in place of ethanol is an insubstantial difference that accomplishes substantially the same function in substantially the same way to achieve substantially the same result as the patented invention.

Respectfully submitted,



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Enclosure

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